REMARKS

Claims 1, 2, and 5-25 remain pending in this Application. Claim 1 has been currently amended.

Applicant has amended Claim 1 to make a minor change to the previously-filed amendment of August 1, 2006, to maintain proper antecedent basis in connection with the term "glucose oxidase". Entry of the amendment is therefore deemed proper and is respectfully requested.

The claims of the Application stand rejected under 35 U.S.C. 103(a) as being unpatentable over Musser et al. (Nature, 11 April 2002, 416, 599-600). The reference is stated to teach that saliva produced by the salivary glands of the caterpillar H. zea, reduces the amount of nicotine released by the tobacco plant Nicotiana tabacum (page 599, first paragraph). The nicotine is toxic to H. Zea and therefore the reduction in nicotine enables the caterpillar to ingest the plant without adverse effect. The reference is further stated to teach that the caterpillar saliva reduces the foliar nicotine levels by over 26% compared with the control (page 599, middle column, lines 9-10) and one can surmise that such reduction in nicotine is sufficient to prevent harm to the caterpillar.

The Office Action concedes that the reference fails to teach the desired amount of treatment required to obtain a non-addictive level of nicotine. Despite a

lack of this teaching, the Office Action states that the number of treatments with glucose oxidase, and the amount of glucose oxidase required to reduce the level of nicotine to the desired level would only require routine experimentation. The Office Action concludes that it would have been prima facie obvious for one skilled in the art at the time of the invention to repeatedly use glucose oxidase from H. zea, or a biochemical source, to treat the tobacco plants without damaging the same and that such repetitive treatments could actually reduce nicotine in the plants to a non-additive level. The rejection is hereby traversed and reconsideration is respectfully requested.

The present invention is directed to a method (as well as tobacco plants so treated) of reducing the nicotine content of a tobacco plant by applying an effective amount of glucose oxidase. The reduction in nicotine is to such an extent that tobacco products made from such plants provide a non-addictive level of nicotine in the central nervous system blood plasma of the user.

The non-addictive level of nicotine in the tobacco product is about 0.01 mg/g of the tobacco plant as indicated on page 3, lines 3-5, and again in the first full paragraph on page 9 of the present application. Thus, the claims of the present application require that the tobacco plant be treated with glucose oxidase in a manner sufficient to reduce the nicotine content to the levels described above. It is these levels that yield a non-addictive level of nicotine in the central nervous system blood plasma as described in U.S. Patent No. 5,713,376 (column 3, lines 38-53). A non-

addictive level of nicotine is a stated object of the invention and a limitation of Applicant's claims.

Musser compares how tobacco plants are affected by a control group of caterpillars (H. Zea) and a test group. The test group of caterpillars have intact spinnerets which enables salivary glucose oxidase to contact the tobacco plants and reduce foliar nicotine levels to an amount (i.e. 26%) which eliminates the deterrence provided by the nicotine against ingestion by the caterpillar. The control group has modified spinnerets in which glucose oxidase cannot contact the plants and therefore there is little if any reduction in nicotine content. Thus, the purpose of the Musser experiment is to show that caterpillars (H. Zea) secrete enough saliva (i.e. glucose oxidase) to reduce the amount of nicotine to a level sufficient to remove the deterrent effect of nicotine against plant ingestion by the caterpillar. 26% is sufficient for this purpose and Musser neither teaches or suggests any further nicotine reduction.

Applicant's invention as claimed is not disclosed or suggested in Musser. The purpose of the experiments in Musser is to show how and to what extent the caterpillar overcomes the toxic effects of nicotine. Once the toxic effect has been diminished to a non-toxic effect (26% reduction of nicotine), nothing further is done and nothing further is suggested. There is no reason offered or motivation derived from Musser to reduce the nicotine level any further, and specifically no reason to engage in the large-fold nicotine reduction required by Applicant's claimed invention. Therefore, any optimum or working range needed to ensure the caterpillar's survival in Musser has already been

achieved, and any further reduction is neither taught nor suggested. In brief, the caterpillar has done its job and that is the end of the Musser experiment.

Applicant acknowledges that glucose oxidase has an effect on nicotine production in tobacco plants. However, Applicant is the first to take this information and apply it to the production of tobacco plants and tobacco products to the extent of achieving non-addictive levels of nicotine. Musser fails to teach or suggest applying glucose oxidase to tobacco plants to an extent that nicotine levels can be reduced to a point where a resulting tobacco product can be made with a non-addictive level of nicotine. More specifically, the reference does not teach or suggest a material feature of the present invention, namely, a reduction in nicotine level by the use of glucose oxidase sufficient to reduce the level of nicotine in a resulting tobacco product to a non-addictive level, nor does the reference provide any means (other than pure speculation) of doing so nor reason to suggest it could be done. For these reasons, Musser would not lead one of ordinary skill in the art to achieve such a large-fold reduction in nicotine levels to produce a tobacco product non-addictive in humans.

In particular, there is no teaching or suggestion in Musser of employing any means of increased glucose oxidase treatment (e.g. concentrated solutions or multiple treatments) for the purpose of achieving further and dramatic reductions in nicotine levels. The 26% reduction results of Musser should be compared with Examples 3 and 4 of the present application in which there is significantly greater reductions in the amount of nicotine present in the treated leaves. Example 3 shows that multiple treatments of the tobacco plants could achieve significantly greater reduction in nicotine

levels as compared to Musser. This is surprising because a) there is no teaching or suggestion that multiple treatments would not have an adverse effect on the treated plants, and b) that further treatments would further reduce the nicotine levels especially in view of the general unpredictability of the behavior of complex biological systems such as a tobacco plant especially when enzymatic reactions are prevalent.

It is well-known among those in the art that it is extremely difficult to model and predict outcomes of classical biological systems and their corresponding reactions over a range of inputs and particularly to predict in vivo enzyme based reactions and corresponding yields. To the contrary, enzymatic based reaction systems are often unpredictable in biological systems. Indeed, in vivo enzyme based reactions are typically non-linear, that is, the amount of enzyme employed does not correlate in a linear manner with the yield of the reaction product obtained.

For example, an article by Gorder in the Ohio State University Research News ("When Biology Gets 'Quirky', Scientists Turn to Math," July 25, 2006 - copy enclosed), acknowledges the longstanding unpredictability of biological systems. The Gorder article discloses that cells sometimes react to medicines in unexpected ways, where "a chemical such as a drug could function very well inside a cell most of the time and then suddenly not work well at all, as if a switch had been flipped." The Gorder article emphasizes that researchers are still a long way from predicting with any degree of certainty what happens inside real biological cells and why reactions involving biological systems are unpredictable, but they do know that "classical biological reactions - - even simple ones - - indicate that these reactions might behave in very quirky ways. This

quirky behavior may be essential to biology itself" indeed Goder urges that "scientists should be cautious when interpreting the results of biochemical experiments".

Although Gorder was published after the filing date of the present application, and therefore is not prior art with respect to the present application, the article is cited as being indicative of the unpredictable nature of the art today, confirming that it was unpredictable at the time of filing of the present application.

Marino ("Chaos and Fractals in Biology and Medicine," presented at Temple University, Center for Frontier Science, March 22, 2000 – copy enclosed), discloses a slide presentation emphasizing that nonlinearity, namely non-proportionality between input and output, exists in biological systems in which enzymes play a major role (see Slide 7: Basis of Biological Nonlinearity). Marino discloses a typical example of a transduction system in the body where force is transmitted by structural proteins, some of which are connected to proteins embedded in the membranes of cells, and converted to produce a chemical signal output. Marino indicates that if the enzymatic activity of one particular enzyme for a particular force has a value X at a given time, the addition of twice the amount of the enzyme will not produce an enzymatic activity value of 2X, due to the inherent nonlinearity of the enzyme based reactions of the biological system. Marino states that "[i]n general, when we alter specific components of complex biological systems the results are unpredictable."

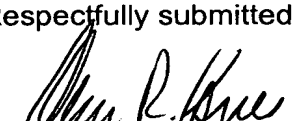
The same inherent unpredictability is expected in biological systems such as plants. Knowing that enzyme based reactions are unpredictable, especially with respect

to yield, there would be no reasonable expectation of success to reduce the nicotine content of tobacco plants to non-addictive levels by simply employing concentrated solutions and/or multiple treatments of glucose oxidase. To the contrary, the skilled artisan would be aware of the inherent unpredictability and not expect further treatments to achieve such a dramatic reduction in nicotine levels. What Musser provides is an invitation to experiment, leaving the skilled artisan to his own devices which is the epitome of non-obviousness.

Applicant has filed concurrently herewith an Information Disclosure Statement to formalize the citation of various references cited herein. Entry of the Information Disclosure Statement and is respectfully requested.

In view of the foregoing, Applicant submits that the present application is in condition for allowance and early passage to issue is therefore deemed proper and is respectfully requested. It is believed that no fee is due in connection with this matter. However, if any fee is due, it should be charged to Deposit Account No. 23-0510.

Respectfully submitted,



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